TITLE: EXPANSION OF THE FMR1 CGG REPEAT IN 2823 BIOPSIED EMBRYO SAMPLES UNDERGOING PREIMPLANTATION GENETIC TESTING

Authors: Olivia Whiting[1], Alessia Schadwell[1], Jenna Miller[2], Chelsea Woody[2], Leoni Xanthopoulou[1], Evi Bakowski[1], N-Neka Goodall[2], Dina Nusblat[2] and Sharyn Lincoln[2]

1. CooperSurgical, London, United Kingdom
2. CooperSurgical, Livingston, New Jersey, USA

Abstract:

Background: Analyses of fragile X messenger ribonucleoprotein 1 gene (*FMR1*) CGG repeat testing and likelihood of expansion have always been done on samples derived from living individuals or prenatal testing.

Objective: To determine if CGG repeat expansion in trophectoderm embryo biopsies is similar to repeat expansion in pre or postnatal samples.

Materials and Methods: Between January 2014 and December 2022, data from 2823 trophectoderm biopsies that underwent PGT-M for FMR1-related disorder via a linkage-based technology (Karyomapping; Illumina, USA), and direct CGG repeat analysis were analyzed. Of those, 2447 biopsies were from FMR1 premutation carriers and 376 biopsies were from FMR1 intermediate carriers.

Results: Analysis of expansion patterns revealed that the premutation allele expanded to a full mutation at the following rates per category group: 0% (0/237) in the maternal premutation group of 55-59 CGG repeats, 3.5% (11/318) in the 60-69 group, 27.3% (56/205) in the 70-79 group, 49.1% (57/116) in the 80-89 group, 97.1% (67/69) in the 90-99 group, and 100% (118/118) in the 100-139 group, 100% (23/23) in the 140-199 group and 100% (59/59) in >200 group. While similar to previously reported percentages, there was a major difference between repeat groups of 80-89 (49.1% for this data set vs 57.8% for Nolin 2003) and 90-99 (97.1% for this data set vs 80.1% for Nolin 2003). Interestingly, 5.6% (14/251) of embryos contracted from the maternal allele size ranging 55-59.

Intermediate alleles expanded to a premutation at the following rates per category group: 0% (0/90) in the maternal intermediate group of 45-50 CGG repeats and 33.0% (36/109) in the 51-54 CGG repeat range. All those that expanded to a premutation had a maternal repeat of 54 CGG repeats.

Conclusion: This unique data set provides a novel insight into the FMR1 CGG repeat patterns at the preimplantation embryo stage and clinical implications of such testing. The data from this study represents larger sample sizes than in previous publications, but expansion percentages are similar to those previously reported (Nolin et al. 2003; Nolin et al. 2015). The ability to distinguish intermediate, premutation and full mutation preimplantation embryos provides more options and information for embryo transfer decisions.

Financial Support: None

References:

Nolin et al. Expansion of the CGG repeat in females with premutation or intermediate alleles. *Am J Hum Genet*. 2003 Feb;72(2):454-64.
Nolin et al. Fragile X full mutation expansions are inhibited by one or more AGG interruptions in premutation carriers. *Genet Med*. 2015 May;17(5):358-64.